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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,788	03/22/2004	Steven C. Quay	03-04US	9945

36814 7590 10/29/2007

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EXAMINER	
HEARD, THOMAS SWEENEY	
ART UNIT	**PAPER NUMBER**
1654	

NOTIFICATION DATE	DELIVERY MODE
10/29/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/805,788	QUAY ET AL.	
	Examiner	Art Unit	
	Thomas S. Heard	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-19* is/are pending in the application.

4a) Of the above claim(s) *3-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/27/2007 has been entered.

The Applicants Amendments to the claims received on 8/27/2007 is acknowledged. The text of those sections of Title 35 U.S. Code not included in the action can be found in the prior office action. Rejections or objections not addressed in this office action with respect to the previous office action mailed 1/8/2007 are hereby withdrawn.

Claim(s) 3-19 are pending. Applicants have added claim(s) 8-19. Claims 3-7 remain withdrawn. Claims 8-19 are hereby examined on the merits.

Claim Rejections - 35 USC § 103

Applicant's arguments with respect to Claims 1 and 2 in the previous office action mailed 5/30/2007 have been considered but are moot in view of the new ground(s) of rejection set forth below on the newly submitted Claims 8-19.

Response to Amendment

The affidavit under 37 CFR 1.132 filed 8/27/2007 is insufficient to overcome the rejection of claims 1 and 2 (now cancelled) but relevant to the new claims 8-19 based upon 35 USC § 103 as set forth in the last Office action because a new search has revealed art that clearly shown Chlorobutanol at concentration even lower that Applicants are claiming.

Applicants have argued:

U.S. Patent No. 5,759,565 states in column 2, lines 39-41 that "Chlorobutanol at 0.6% in calcitonin nasal pharmaceutical compositions showed insufficient activity against the test fungus Pen. steckii." I believe that the reference U.S. Patent No. 5,759,565 would have been understood by a person of ordinary skill in the art on its publication date of June 1998 to have taught in column 2, lines 35-67 that Chlorobutanol had been tested in some calcitonin nasal pharmaceutical compositions, and was found in those compositions to have insufficient activity at a concentration of 0.6% against the well know test microorganism Pen. steckii. It is my opinion that a person of ordinary skill in the art in 1998 would have known in general that a preservative is less effective against microorganisms when used at a lower concentration. It would therefore have been understood by a person of ordinary skill in the art in 1998 based on the teachings of the reference U.S. Patent No. 5,759,565 that it would have been doubtful that Chlorobutanol could successfully be used at any concentration less them 0.6% as a preservative in a calcitonin nasal pharmaceutical composition. I believe that the reference U.S Patent No. 5,759,565 would have been understood by a person of ordinary skill in the art on its publication date of June 2, 1998 to have taught that an alternative preservative, namely benzalkonium chloride, was useful as a preservative in calcitonin nasal pharmaceutical compositions.

Applicant's arguments have been carefully considered and in light of the new reference of Grebow et al US Patent 5,026,825, the prior art shows that Chlorobutanol was used in combination with calcitonin, and the concentration of Chlorobutanol as 0.1% w/v. This prior art reference clearly indicates and teaches Chlorobutanol at lower concentrations that 0.6% and provides clear teaching to lower the concentration of

Chlorobutanol. Finally, the prior art reference clearly intends the use of Chlorobutanol to be that of a preservative providing string motivation and reasonable expectation of success to lower the concentration of Chlorobutanol below that of 0.6%. Therefore, the prior art reference is deemed sufficient to rebut the Applicant arguments.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-11, 13-15, and 17-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-11, 13-15, and 17-19 add limitations that does not follow with the definition of a composition which is what is claimed in Claims 8, 112, and 16. Merriam-Webster defines composition (http://www.webster.com/dictionary/composition) as "a product of mixing or combining various elements or ingredients." The nasal spray apparatus is more an intended use rather than a particular part of the composition itself.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said

subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Armour Pharmeceutical Company (EP 0115627) referred to as APC, and Moise Azria et al U.S. Patent 5,759,565, both from Applicant's IDS and made of record in th previous office action, and Grebow et al US Patent 5,026,825.

In instantly claimed invention is drawn to a composition comprising: an aqueous solution of calcitonin salmon at a concentration of 2200 International Units (I.U.) per ml or 0.0355% w/w; Chlorobutanol at a concentration of about 0.25% weight/weight; sodium chloride at a concentration of 0.85% weight/weight; and hydrochloric acid in an amount sufficient to adjust the pH of the solution to 3.5; wherein the composition is suitable for intranasal administration in humans.

Azria et al teaches calcitonin in a saline solution (tonicity) of 0.75 % w/w which is about 0.85% at a pH of 3 to 5 where the pH has been adjusted with HCl. The amount of calcitonin used in the invention is taught to be between 150 and 8,000 MRC units (I.U. of Activity) of salmon calcitonin, readable on Applicants 2200 I.U. per ml. The composition is taught to be to be stored under an inert Nitrogen atmosphere for stability of the calcitonin. Chlorbutanol is also taught as being use in the nasal composition but suffers from some drawbacks when used at 0.6%. Azria et al does not teach the use of Chlorbutanol at ranges lower than that of 0.6%, see, Column 4 and lines 6-20; column 6 and lines 11-18; and column 7 and lines 32-37.

APC teaches pharmaceutical composition for nasal administration comprising calcitonin at a concentration range of 1 to 150 ug/ml where the concentration and

dosage levels of calcitonin are with a potency of about 4000 I.U. per mg, well within the range taught by Azria et al and instantly claimed. APC teaches the use of a Tonicity Adjuster in the range of 0.01-.5 %w/v readable upon the saline solution of Azria et al. APC also teaches the use of Chlorobutanol (a preservative) in the range of 0.001-2.0 % w/v which is instantly claimed, see page 5 and line 5-18 and page 6 for the additive ranges.

Grebow et al, US Patent 5,026,825 teaches an intranasal composition comprising from about 0.0001% W/V to about 15% W/V of a polypeptide salmon calcitonin or having calcitonin activity (potency of from about 100 to about 10,000 international units per mg of polypeptide readable upon Applicant 0.355% w/w of Claim 8 and 2200 I.U of Claim 12 and 16, see Claims 1-7 of '825. Grebow further teaches the preservative Chlorobutanol in ranges from 0.5-1.0 and in Example 9, teaches Chlorobutanol at 0.1% w/v. Note that the examiner is taking the mass of water to be 1 g/ml therefore which makes the translation fro w/v% to be essentially identical to that of w/w%.

It would have been obvious at the time of the instantly claimed invention to optimize the concentration of Chlorobutanol %w/v for any deleterious effects as the art clearly teaches the use of Chlorobutanol in combination with calcitonin and at concentrations as low as 0.1% w/v. It would have been obvious to one skilled in the art at the time of invention to determine all operable and optimum components in the claimed composition of U.S. Patent No. Armour Pharmeceutical Company (EP 0115627) and Moise Azria et al U.S. Patent 5,759,565, because the component % w/v

are an art-recognized result-effective variable that is routinely determined and optimized in the composition arts. One would have been motivated to modify the composition as taught by both APC, Azria et al, and Grewbow to optimize the concentration parameters to eliminate undesirable effect of any given component and or enhance the effect of a given component as calcitonin, saline, Chlorobutanol, as the art teaches their combination and use. Given the intended use of the composition is for nasal administration, putting the composition into a sprayer is obvious on its face. The parameters of the actuator tip, spray pattern, droplet size etc... are also art-recognized result-effective variables that is routinely determined and optimized for nasal administration in the composition arts. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Applicant's arguments have been carefully considered but are not deemed persuasive. Applicants have argued:

Applicant respectfully responds that Examiner has not supplied a primafacie case for obviousness because Azria et al. teach away from use of chlorobutanol in a calcitonin solution. Applicant respectfully submits that Examiner ignores the factual teaching ofAzria et al., as discussed in previous papers, that chlorobutanol showed insufficient activity against a test fungus. The single point concentration recited in the '565 patent ofAzria et al. was a sufficient basis to Azria et al. themselves as being a reason not to select chlorobutanol. In view of the fact, as stated in Azria et al., that many possible preservatives could have been selected for testing in a calcitonin solution, yet only chlorobutanol was shown to be questionable, a person of ordinary skill in the art would not have been motivated to select and test chlorobutanol for use as a preservative in a calcitonin solution, regardless of other factors. The reference EP '627 is not pertinent to this issue since it provided no specific factual evidence on which a

person of ordinary skill in the art could have relied in 1998 when the unsuitability of chlorobutanol was factually shown by Azria et al. Thus, Applicant respectfully submits that a person of ordinary skill in the art in 1998 would not have been motivated to select and test chlorobutanol as a preservative in a calcitonin solution in view ofAzria et al. In sum, the specific factual teaching of Azria et al. is that chlorobutanol is doubtful as a preservative, but benzalkoniumn chloride works well. This teaches away from selecting chlorobutanol for testing as a preservative in a calcitonin solution.

In light of the newly added reference, the use of Chlorobutanol at lower concentrations rebuts the alleged teaching away in EP '627 and clearly puts the range of Chlorobutanol within the scope of routine optimization as the concentration used is lower than that of the Applicants. Therefore, the new rejection stands in light of the arguments.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas S. Heard whose telephone number is (571) 272-2064. The examiner can normally be reached on 9:00 a.m. to 6:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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